

## EDITORIAL COMMENT

# Cardiac Resynchronization Therapy in Patients With Intermittent Atrial Arrhythmias



## Will Cardiac Resynchronization Therapy Be Good for All?\*

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Cardiac resynchronization therapy (CRT) is an established treatment for symptomatic patients with heart failure (HF), a prolonged QRS duration, and reduced ejection fraction (EF).

The latest 2013 European Society of Cardiology Guidelines on cardiac pacing and cardiac resynchronization therapy (1) support recommendations for the use of CRT in patients with QRS duration of  $\geq 120$  ms and EF  $\leq 35\%$ , to reduce the risk of HF hospital stay and premature death. In the Guidelines were considered patients in sinus rhythm and patients with permanent or long-standing persistent atrial fibrillation (AF) with hemodynamic indication for CRT or with a fast ventricular rate justifying a strong rate control strategy with an atrioventricular (AV) junction ablation.

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The MUSTIC (MULTIsite STimulation in cardiomyopathy) trial (2) included 59 patients with HF and reduced EF with persistent/permanent AF, slow ventricular rate, permanent pacing, and a paced QRS duration  $>200$  ms. There was a high drop-out (42%), and no difference in primary endpoint of 6-min walking distance. The per-protocol analysis including only patients with a biventricular pacing rate  $>85\%$  did show a slight but significant improvement in functional status at 6-month and 1-year follow-up.

The RAFT (Resynchronization/Defibrillation for Ambulatory Heart Failure) trial (3) included 229 patients with

permanent AF or atrial flutter either with controlled ventricular rate or with planned AV junction ablation. The analysis showed a significant interaction between baseline rhythm and treatment effect.

In the APAF (Ablate and Pace in Atrial Fibrillation) trial (4), patients were treated with CRT and AV junction ablation; in the subgroups of patients with low EF, New York Heart Association functional class  $\geq III$ , and QRS  $\geq 120$  ms, CRT significantly reduced the primary endpoint, including death from HF, hospital stays, or worsening of HF. The same findings were observed in the left ventricular-based cardiac stimulation PAVE (Post AV Nodal Ablation Evaluation) trial (5).

Wilton et al. (6), in a meta-analysis from 33 observational studies with 22.5% AF patients, compared outcomes in patients with and without AF receiving CRT. They reported in patients with AF an increased risk of nonresponse to CRT (34.5 vs. 26.7%;  $p = 0.01$ ) and all-cause mortality (10.8 vs. 7.1%/year;  $p = 0.001$ ). The AV junction ablation seemed favorable with a lower risk of clinical nonresponse (risk ratio: 0.40;  $p < 0.001$ ) and a reduced risk of death.

In addition, Santini et al. (7) evaluated the correlation between atrial tachycardia (AT) or AF and clinical outcomes, such as survival or HF hospital stays, in a large population of patients with CRT implantable cardioverter-defibrillators (CRT-D), according to 5 AT/AF burdens, whose lengths were  $>10$  min,  $>6$  h,  $>24$  h,  $>7$  days, and  $>6$  months. Patients with persistent or permanent AT/AF had higher incidences of the composite endpoint or HF hospital stay when compared with patients in sinus rhythm.

It has been shown that the greatest improvement and reduction in mortality occur with a biventricular pacing  $>98\%$  (8). Therefore, failure of biventricular capture might explain the lack of benefit of CRT in patients with persistent/permanent AF (9).

In this issue of the *Journal*, Ruwald et al. (10) assessed the effect of intermittent atrial tachyarrhythmias (IAT) before and during CRT-D in 1,241 patients of the MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) (11). The study showed that the percentage of biventricular pacing was similar in both group. The cumulative endpoint of HF, hospital stay, and death was significantly reduced in patients treated with CRT-D with and without a history of IAT, compared with ICD-only therapy. Unfortunately, the investigators were unable to detect atrial arrhythmias with ventricular rate  $<180$  beats/min and provided no data on arrhythmias burden.

With the current level of knowledge, how should clinicians treat patients with AT/AF and HF?

In our opinion, all patients who meet the recommended criteria for CRT, despite their atrial arrhythmias burden, should receive this therapy. Gasparini et al. (12) demonstrated that patients with permanent AF, treated with CRT, and candidates for AV junction ablation gain the same benefit as patients in sinus rhythm. The potential benefits must be balanced against the risks associated with creating pacemaker dependency. Thus, AV junction ablation can be

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performed during CRT implantation or after correct lead and device functioning assessment.

Moreover, the EuroHeart Failure survey reported that up to 45% of patients with HF and sinus rhythm also presented with intermittent or permanent AF (13). Ruwald has shown that patients with or without a history of IAT had significant reduction in left atrial volume within 1 year of follow-up. Favorable reverse remodeling of the left atrium with CRT was associated with a significant reduction in risk of subsequent atrial tachyarrhythmias (14). A particular aspect of AF patients is that AF rhythm with a fast ventricular rate and irregularity might interfere with adequate biventricular pacing delivery (1). Device diagnostics allow a continuous monitoring of cardiac arrhythmias, evaluation of AT/AF occurrence and duration, and information about lead, and device function. These web-based care alerts might determine clinical re-evaluation of current treatment to optimize rhythm or rate control.

Moreover, the newest devices give us information also on reduced physical activity or volume overload. All these data are helpful to detect patients with high risk of worsening clinical condition, to improve medical treatment and CRT device programming, and avoid further hospital stay and progression of HF.

In conclusion, the beneficial effects of CRT in patients with atrial tachyarrhythmias are related to the percentage of biventricular pacing and to the burden of AT/AF. To reduce interference on biventricular capture, we can optimize medical therapy and, in case of AF with inadequate heart rate control, perform AV junction ablation.

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